REMARKS

Claims 1 and 3 to 11 are currently pending and under examination in the application. By the present amendment, claims 1 and 3 are amended. Support for this amendment is provided throughout the specification as filed and does not constitute new matter. This amendment is made without acquiescence to the rejection and without prejudice to pursuing the encompassed subject matter in a related divisional, continuation, or continuation-in-part application.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 3-11 stand rejected under Section 112, first paragraph, as allegedly failing to comply with the written description requirement. In particular, the Examiner asserts that the instant specification does not provide written description support for the term "single stranded."

Without acquiescence to this basis of rejection, Applicants have amended the claims to remove the term "single-stranded," thus obviating the basis for this rejection. Accordingly, Applicants respectfully request that it be withdrawn.

Rejections under 35 U.S.C. § 103

A. The Examiner has maintained the rejection of claims 1 and 3 to 5 under 35 U.S.C § 103(a) for alleged obviousness over Herman *et al.* (U.S. Patent No. 5,786,146, issued July 28, 1998) in view of Gerdes *et al.* (U.S. Patent 6,291,166, issued Sep. 18, 2001). More specifically, the Examiner asserted that Herman *et al.* describe deamination performed in solution, followed by binding of the deaminated nucleic acid to a solid phase. The Examiner further asserted that Gerdes *et al.* disclose solid phase manipulation and analyses of nucleic acids, including enzyme recognition, hybridization and amplification. The Examiner then asserted that one of ordinary skill in the art would have been motivated to apply a solid phase bound DNA as taught by Gerdes *et al.* in the method of Herman *et al.* because, as taught by Gerdes *et al.*, a solid phase bound nucleic acid can be directly and conveniently manipulated and can be applied in various ways. The Examiner further asserted that such a combination would have been *prima facie* obvious at the time of filing.

Applicants traverse this basis of rejection and submit that the Examiner has not established a *prima facie* case of obviousness. The Examiner must at a minimum demonstrate that the cited references teach or suggest all the claim features, and even assuming, *arguendo,* that the references teach each claim feature, the Examiner must provide an explicit, apparent reason to practice these features in the fashion claimed by the Applicants with a reasonable expectation of success. *See KSR v. Teleflex, Inc.,* No. 04-1350 at 4, 14 (U.S. Apr. 30, 2007) ("A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art"). As previously submitted, the Examiner has not shown that the cited references teach or suggest performing a deamination reaction on a nucleic acid bound to a solid phase, and the Examiner has not established the requisite motivation to practice the presently claimed subject matter with a reasonable expectation of success.

Neither of the cited references teaches or suggests performing a deamination reaction on a nucleic acid bound to a solid phase. The Examiner has acknowledged that Herman *et al.* fail to teach or suggest the active, recited step of performing a deamination reaction on a nucleic acid bound to a solid phase, and Gerdes *et al.* fails to teach or suggest performing a deamination reaction. Instead, Gerdes *et al.*, at best, mention the use of solid phase matrices in purification methods to irreversibly capture RNA or DNA, and solid phase manipulation and analyses including enzyme recognition, hybridization and amplification. It is important to understand that these types of solid phases manipulations are very different than deamination, particularly since they do not involve chemical alteration of the nucleic acid. As noted previously, the utility of the invention described in Gerdes *et al.* requires that the nucleic acid is neither altered nor exhausted during analysis (*see, e.g.*, column 2, lines 45-47 of Gerdes *et al.*). This utility, however, in no way relates to chemically modifying nucleic acid molecules as in the presently claimed methods. Gerdes *et al.*, therefore, fail to teach or suggest the use of solid phase immobilization, as described therein, with a nucleic acid modification reaction, such as with the bisulfite reaction recited in the instant claims. Accordingly, the cited references fail to teach deamination of a nucleic acid bound to a solid support.

Furthermore, even assuming *arguendo* that each feature recited in the instant claims was known in the art, the Examiner has still failed to establish a *prima facie* case of obviousness, since the Examiner does not provide a sufficient reason as to why the skilled artisan would combine the teachings of the prior art to practice the claimed invention with any reasonable expectation of success. In fact, Applicants submit that there are numerous reasons why the skilled artisan would not have believed that a deamination reaction could be successfully performed on a nucleic acid bound to a solid phase, at the time the instant application was filed.

First, Applicants maintain the position that the skilled artisan would not have expected bisulfite ions to be able to physically interact with the cytosines in DNA bound to a solid phase, since it was believed that single-stranded DNA interacted with a solid phase as if it were participating in base-pairing. This understanding on the part of the skilled artisan is clearly set forth in the previously submitted Declaration of Dr. Markert-Hahn (*see, e.g.*, Items 5 and 12 of the Declaration with the Amendment/Response filed April 15, 2008) and Declaration of Matthias Ballhause (submitted with the Amendment/Response filed February 12, 2010), which evidences that at the time the instant application was filed, one of skill in the art would not have reasonably expected that a denatured nucleic acid bound to a solid phase could have been subjected to bisulfite treatment. In particular, Dr. Ballhouse, experienced in the field, asserted that it was the common view that solid phase-bound DNA would not be susceptible to bisulfite modification, because at the time it was believed that bisulfite ions reacted only with pyrimidine bases not involved in base-pairing, and it was believed that the binding of denatured DNA to a solid phase involved interactions similar to base-pairing.

Applicants submit that the Examiner does not appear to be giving these Declarations sufficient consideration, particularly with respect to the specific type of reaction being performed according to the presently claimed method, *i.e.*, deamination. Instead, the Examiner appears to have taken the position that because Gerdes *et al.* allegedly describe nucleic acid bound to a solid phase as being able to participate in various analyses, including enzyme recognition, hybridization and amplification, one of skill in the art would expect that it could also participate in other desirable chemical reactions. Applicants submit that a mere general suggestion to manipulate solid phase bound nucleic acid does not render obvious all specific

types of manipulations, let alone the specific chemical reaction performed according to the presently claimed method. Furthermore, the Declaration of Dr. Ballhouse provides explicit reasons as to why one of skill in the art would not have expected to be able to perform deamination on solid phase-bound nucleic acids, including the fact that it was believed that bisulfite ions could only interact with pyrimidine bases not involved in base-pairing. Instead, the mere fact that solid phase-bound nucleic acids could participate in hybridization reactions does not imply that they could also interact properly with bisulfite ions and undergo deamination. Clearly, this was the belief at the time the instant application was filed, as discussed in the previously submitted Declarations. Thus, Applicants respectfully request that the Examiner reconsider this issue in view of the Declarations.

Moreover, Applicants submit that Gerdes *et al.* actually teaches away from the presently claimed method. In particular, at column 4, lines 7-10, Gerdes *et al.* describe that nucleic acids may be bound to a solid phase in single-stranded form as opposed to double-stranded form by adjusting conditions to an alkaline pH or a high chaotropic salt conditions. However, bisulfite conversion is performed under acidic conditions (*e.g.*, pH 5.0; *see, e.g.*, Example 5 at 5.3 of the instant application). Accordingly, the skilled artisan, believing that deamination can only be performed on single-stranded nucleic acids, would have understood from Gerdes *et al.* that it might not be possible to bind nucleic acids to a solid phase under conditions favorable for performing deamination.

In addition, Applicants submit that there are additional reasons why the skilled artisan would not have believed that the teachings of Herman *et al.* with respect to deamination could be combined with the teachings of Gerdes *et al.* regarding solid phase nucleic acid manipulations to perform the presently claimed method with any reasonable expectation of success. In particular, Gerdes *et al.* describe binding of DNA to solid phases via electrostatic interaction (*see, e.g.*, column 2, lines 66-67: "Specifically, DNA binds to solid phases that are electropositive and hydrophilic" and column 4, lines 1-4: "highly electropositive solid phase materials"). However, at the time of filing the instant application, the skilled artisan would have been aware of several problems that one would expect in connection with performing the presently claimed method on nucleic acids electrostatically coupled to a solid phase.

First, the skilled artisan would have appreciated that the binding strength between the nucleic acids and the solid phase directly correlates with the length of the nucleic acid molecule due to the absolute number of electric charge interactions. Thus, the absolute binding strength between the nucleic acid and the solid phase is lower for shorter nucleic acids. Moreover, the skilled artisan would have understood that given the reaction conditions used during deamination (high temperatures over a long period of time, low pH, *e.g.*, 50°C for 16h, pH 5.0; *see, e.g.*, Example 5 at 5.3 of the instant application), the nucleic acid would be present as a complex mixture of very short fragments (*see, e.g.*, Abstract and Figure 3 of Grunau *et al.*, *Nucleic Acids Research*, 2001, Vol. 29, No. 13, pp. 1-7, attached). Accordingly, the skilled artisan would have expected that the strength of electrostatic interactions between bisulfite-treated nucleic acids and the solid phase would likely not be sufficient to ensure stable binding. Therefore, the skilled artisan would have no reasonable expectation of being able to perform deamination on solid phase-bound nucleic acids or being able to practice the presently claimed method.

Furthermore, the skilled artisan would have been aware that the bisulfite reaction is performed under high salt conditions (*e.g.*, 2M sodium bisulfite; *see, e.g.*, Example 5 at 5.3), and that positively charged ions present under such high salt conditions weaken the electrostatic binding of anionic nucleic acids to an electropositive solid phase. Therefore, the skilled artisan would have been concerned that the strength of electrostatic interactions between the nucleic acids and the solid phase would likely not be sufficient to ensure stable binding. Thus, the skilled artisan would have no reasonable expectation of being able to perform deamination on solid phase-bound nucleic acids or being able to practice the presently claimed method.

Clearly, based on the above, the skilled artisan would have no reasonable expectation of being able to successfully combine the teachings of Gerdes *et al.* and Herman *et al.* to achieve the presently claimed methods. Moreover, the skilled artisan would also have no motivation to attempt to do so, and, in fact, would be dissuaded from even trying to do so, particularly in view of the teachings of Gerdes with respect to the conditions for binding single-stranded nucleic acids to a solid phase. It also would not be obvious to even try to combine the teachings of these reference, because it was not known at the time the instant application was

filed that (i) short bisulfite-treated DNA fragments could stably bind to a solid phase via electrostatic interactions, and (ii) high salt concentrations present during bisulfite conversion do not eliminate this binding.

Applicants respectfully submit that the Examiner has not established that the instant claims are obvious over the cited references, alone or in combination, and, therefore, respectfully requests that this basis of rejection be withdrawn.

B. The Examiner has maintained the rejection of claims 6 to 11 under 35 U.S.C. § 103(a) for alleged obviousness over Herman *et al.* in view of Gerdes *et al.* (as applied to claims 1 and 3 to 5 in section A above), and further in view of Weindel *at al.*, essentially for the same reasons enunciated in previous office actions.

For the reasons discussed in section A above, Applicants submit that Herman *et al.* and Gerdes *et al.* fail to teach or in any way suggest the active recited step of incubating the solid phase bound nucleic acid in the presence of sulfite ions whereby the nucleic acid is deaminated, as recited in the instant claims. Weindel *at al.* also does not remedy this deficiency, as this reference is silent with respect to performing deamination reactions on solid phase bound nucleic acid. In fact, Weindel *at al.* is limited to teaching the use of the magnetic glass particles described therein for either nucleic acid purification protocols or standardized nucleic acid amplification reactions. Thus, in failing to teach or suggest each feature of the instant claims, the cited references, alone or in combination, fail to establish a *prima facie* case of obviousness.

Moreover, even if a person skilled in the art at the time of filing combined the methods of Herman *et al.* Gerdes *et al.*, and Weindel *at al.*, the person would not arrive at the presently claimed subject matter with any reasonable expectation of success. The combination proposed by the Examiner simply does not teach a person skilled in the art to perform deamination reactions on solid phase, as recited in independent claim 1, but instead teaches that person to perform such reactions in solution, in effect teaching away from the presently claimed methods. Thus, a person skilled in the art at the time of filing would have had to embark on a whole new line of experimentation to arrive at the presently claimed method, which would have

required that person to go against the expectations in the art at the time of filing, as discussed in section A above.

Given the deficiencies in Herman *et al.*, Gerdes *et al.*, and Weindel *at al.*, these references, alone or in combination, fail to render the instant claims obvious. Applicants respectfully request withdrawal of this basis of rejection.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Applicants submit that the claims in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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